

From the INTERNATIONAL BUREAU

Prior Art

PCT

NOTIFICATION CONCERNING
TRANSMITTAL OF COPY OF INTERNATIONAL
PRELIMINARY REPORT ON PATENTABILITY
(CHAPTER I OF THE PATENT COOPERATION
TREATY)

(PCT Rule 44bis.1(c))

To:

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Date of mailing (day/month/year)
27 July 2006 (27.07.2006)

Applicant's or agent's file reference
P32890A/GTO/BPU RTH

IMPORTANT NOTICE

International application No.
PCT/GB2004/004788

International filing date (day/month/year)
15 November 2004 (15.11.2004)

Priority date (day/month/year)
14 November 2003 (14.11.2003)

Applicant

THE QUEEN'S UNIVERSITY OF BELFAST et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

COPY

The International Bureau of WIPO
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

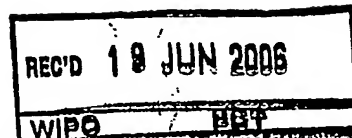
(PCT Rule 44bis)

Applicant's or agent's file reference P32890A/GTO/BPU	FOR FURTHER ACTION	See item 4 below
International application No. PCT/GB2004/004788	International filing date (<i>day/month/year</i>) 15 November 2004 (15.11.2004)	Priority date (<i>day/month/year</i>) 14 November 2003 (14.11.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant THE QUEEN'S UNIVERSITY OF BELFAST		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).																								
2.	This REPORT consists of a total of 9 sheets, including this cover sheet.																								
In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.																									
3.	<p>This report contains indications relating to the following items:</p> <table style="width: 100%;"> <tr> <td style="width: 10%; text-align: center;"><input checked="" type="checkbox"/></td> <td style="width: 30%;">Box No. I</td> <td style="width: 60%;">Basis of the report</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	<input checked="" type="checkbox"/>	Box No. I	Basis of the report	<input type="checkbox"/>	Box No. II	Priority	<input checked="" type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input checked="" type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input type="checkbox"/>	Box No. VI	Certain documents cited	<input type="checkbox"/>	Box No. VII	Certain defects in the international application	<input type="checkbox"/>	Box No. VIII	Certain observations on the international application
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4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).																								

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Date of issuance of this report 17 July 2006 (17.07.2006)</td> <td style="width: 50%;">Authorized officer</td> </tr> <tr> <td></td> <td style="text-align: center; vertical-align: middle;">Nora Lindner</td> </tr> <tr> <td colspan="2">e-mail: pt02@wipo.int</td> </tr> </table>	Date of issuance of this report 17 July 2006 (17.07.2006)	Authorized officer		Nora Lindner	e-mail: pt02@wipo.int	
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	Nora Lindner						
e-mail: pt02@wipo.int							

PATENT COOPERATION TREATY



From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference see form PCT/ISA/220		FOR FURTHER ACTION See paragraph 2 below	
International application No. PCT/GB2004/004788	International filing date (day/month/year) 15.11.2004	Priority date (day/month/year) 14.11.2003	
International Patent Classification (IPC) or both national classification and IPC C07K14/82, C07K14/705, C07K16/32, C12N5/12, G01N33/574, A61K39/395, C12N15/11, A61P35/00			
Applicant THE QUEEN'S UNIVERSITY OF BELFAST			

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application



2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

<p>Name and mailing address of the ISA:</p>  <p>European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465</p>	<p>Authorized Officer</p> <p>Loubradou, G</p> <p>Telephone No. +49 89 2399-8543</p> 
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/004788

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☒ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☒ in written format
☒ in computer readable form
 - c. time of filing/furnishing:
☒ contained in the international application as filed.
☒ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/004788

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1-12, 14, 16 (all partially) and 13,15, 17-36 (all completely)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 1-12, 14, 16 (all partially) and 13,15, 17-36 (all completely)
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/004788

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☒ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-12 , 14. 16 (all partially)

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	3, 6, 7, 10
	No: Claims	1, 2, 4, 5, 8, 9, 11, 12, 14, 16
Inventive step (IS)	Yes: Claims	
	No: Claims	1-12, 14, 16
Industrial applicability (IA)	Yes: Claims	1-11, 16
	No: Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

- D1: DATABASE EMBL [Online] 14 November 1997 (1997-11-14), "Homo sapiens transmembrane protein Jagged 1 (HJ1) mRNA, complete CDs." XP002321955 retrieved from EBI accession no. EM_PRO:AF028593 Database accession no. AF028593
- D2: HAQUE RAQEEB ET AL: "Demonstration of Notch-1 and Delta-like expression in human glioma cell lines and cytotoxic effect of Notch-1 inhibition." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, vol. 44, July 2003 (2003-07), page 1310, XP001205455 & 94TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH; WASHINGTON, DC, USA; JULY 11-14, 2003 ISSN: 0197-016X
- D3: SUZUKI NORIAKI ET AL: "THE EXPRESSION OF NOTCH FAMILY GENES IN HUMAN PANCREATIC CANCER." DIGESTIVE DISEASE WEEK ABSTRACTS AND ITINERARY PLANNER, vol. 2003, 2003, page Abstract No. M1015, XP009044633 & DIGESTIVE DISEASE 2003; FL, ORLANDO, USA; MAY 17-22, 2003
- D4: BOOTH CHRISTINA L ET AL: "Expression of Jagged/Notch family members in diverse tumors in vivo: Association in vitro with a transformed phenotype" PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, no. 41, March 2000 (2000-03), pages 474-475, XP009044602 & 91ST ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH.; SAN FRANCISCO, CALIFORNIA, USA; APRIL 01-05, 2000 ISSN: 0197-016X
- D5: WO 98/58958 A (UNIVERSITY OF WASHINGTON; THE CHILDREN'S HOSPITAL OF PHILADELPHIA; LI,) 30 December 1998 (1998-12-30)
- D6: LI L ET AL: "THE HUMAN HOMOLOG OF RAT JAGGED1 EXPRESSED BY MARROW STROMA INHIBITS DIFFERENTIATION OF 32D CELLS THROUGH INTERACTION WITH NOTCH1" IMMUNITY, CELL PRESS, US, vol. 8, January 1998 (1998-01), pages 43-55, XP002915687 ISSN: 1074-7613

Re Item IV.

The separate inventions/groups of inventions are:

- Invention 1: claims 1-12 , 14, 16 (all partially)
Nucleic acids comprising the sequence shown in SEQ ID N°1 and the related subject-matter.
- Invention 2: claims 1-12, 14, 16 (all partially)
Nucleic acids comprising the sequence shown in SEQ ID N°2 and the related subject-matter.
- Invention 3: claims 1-12 , 14, 16 (all partially)
Nucleic acids comprising the sequence shown in SEQ ID N°3 and the related subject-matter.
- Invention 4: claims 12, 14 and 16 (all partially), and 13, 15, 17 and 18 (all completely)
Method of producing an antibody/hybridoma involving G-CCM cells of ECACC deposit N° 86022702 and the corresponding antibody/hybridoma from EACC deposit N° 03073001
- Invention 5: claims 19 and 20 (all completely) and 23-25 (all partially)
Method of detecting an astrocytoma cell and the corresponding kit.
- Invention 6: claims 21 and 22 (all completely) and 23-25 (all partially)
Method of detecting a primary breast carcinoma cell and the corresponding kit
- Invention 7: claims 23-25 (all partially)
Diagnostic kit for diagnosing the presence of malignant melanoma secondary tumour cells
- Invention 8: claims 26-31
Antibodies comprising a therapeutic ligand, therapeutic antibodies and a method of treating cancer using antibodies
- Invention 9: claims 32-36
Anti-sense molecules and use thereof in a method of treating cancer

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for

the following reasons:

According to Rule 13.1 PCT, an international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art (Rule 13.2 PCT).

The only technical feature shared by the 9 inventions listed above is that they are related to nucleic acids/proteins derived from the human Jagged1 gene. The nucleic acid encoding the human JAGGED1 protein is known in the art and said nucleic acid comprises the sequences of SEQ ID N°1 and SEQ ID N°2 of the present application (see D1). Therefore, said technical feature is not novel.

The inventions 5 to 7 also share the technical feature of being methods to detect cells associated with cancer involving an antibody directed against a protein derived from the human Jagged1 gene. However, it is known in the art that Jagged1 is expressed in some glioma cell lines (see D2), in human pancreatic cancer tissues (see D3) and in "human tumors of diverse origin", including breast carcinomas (see D4). In D3 the expression of Jagged 1 was examined by immunohistochemistry implying the use of an antibody directed against Jagged1. The attention of the applicant is further drawn to the fact that antibodies directed against Jagged1 are well known in the art (see for example D5: WO9858958, page 22 line 28 to page 24 line 22 or D6, page 52, right-hand column, the paragraph entitled "Anti-hJagged1 Monoclonal antibody"). Therefore, said technical feature is not novel in view of D3 or completely obvious in view of D2 and D4.

In view of the above reasoning, it appears clearly that the technical features shared by the 9 inventions of the present application are not novel. Therefore, the present application does not meet the requirement of unity of invention and corresponds to 9 separate inventions (Rule 13 PCT).

Re Item V.

1. D1 discloses a nucleic acid comprising the sequence of SEQ ID N°1 of the present application and the corresponding protein.
Therefore, D1 anticipates claims 1, 2, 4 and 5 of the present application (Article 33(2) PCT).

Dependent claims 3, 6 and 7 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, see D1.

2. D5 discloses a Jagged1 nucleic acid comprising a sequence almost identical to the sequence of SEQ ID N°1 (99.8% sequence identity) (see the Fig 1A of D5). The corresponding coding sequences differ at two positions and in both cases the same amino acid is encoded by the different codons. Therefore, the protein disclosed in the Fig 1 A of D5 is encoded by a nucleic acid comprising the sequence of SEQ ID N°1 of the present application.
D5 further discloses monoclonal and polyclonal antibodies directed against the protein having the sequence shown in Fig 1A and methods to generate said antibodies (see D5, page 22 line 28 to page 24 line 22).
Therefore, D5 anticipates claims 4, 8, 9, 11, 12, 14 and 16 (Article 33(2) EPC).

The dependent claim 10 does not contain any feature which, in combination with the features of any claim to which it refers, meet the requirements of the PCT in respect of inventive step, see D5 (page 22 line 28 to page 24 line 22 and Fig 1A).

3. Claims 12 and 14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).